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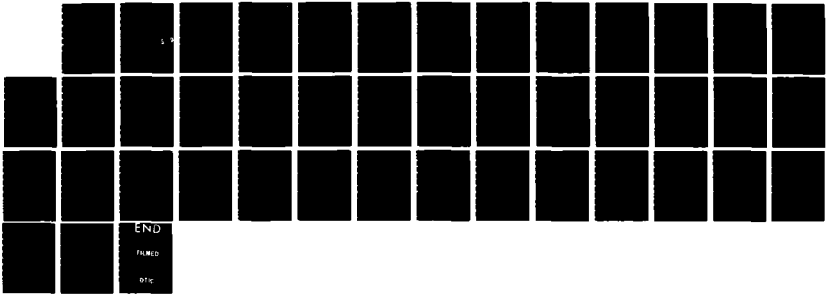

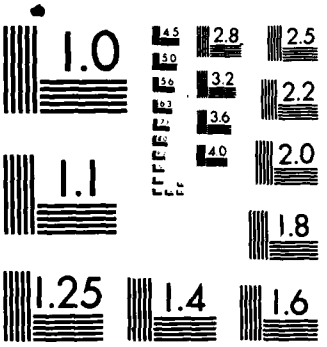

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Recent progress in the interaction of theoretical ideas and experimental results that relate to learning and memory is discussed. Consideration is given, in particular, to the effects of the neurotransmitters GABA, Norepinephrine and Acetylcholine on the development of circuitry in visual cortex.

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Local and Global Factors in Learning

Leon N Cooper

Department of Physics

and

Center for Neural Science

Brown University

Providence, Rhode Island 02912

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The title of this volume suggests how far we have come. No one would ever have contested the importance of understanding the brain, the interest of identifying how learning takes place or how and where memory is stored. Since Artistotle (who identified heart as the seat of intellect reserving for brain the function of cooling the body) the brain has generally been thought to be the source of thought, the location of memory, the physical basis of mind, soul, consciousness, and self-awareness: all that make us distinct and human. What has changed is the belief, becoming more and more prevalent, that the time has come. Not only is the problem fascinating and important but, also, the tools are available. We can do it now.

For many years we have heard talk about possible modification of synapses between neurons as the physiological basis of learning and memory storage. These relatively vague ideas are becoming more precise. Insight into the molecular basis of synaptic modification is begining to appear; the role of possible global controllers such as Norepinephrine and Acetylcholine is being clarified; and a mathematical structure for the network of neurons is rapidly evolving.

What I would like to present here is a brief summary of some recent theoretical and experimental results related to plasticity in visual cortex, and presumably related to the changes that take place in the nvervous system when learning occurs and when memory is stored. More important than the details, I hope to convince you is that what is being presented provides us with a language in which questions concerning memory and learning can be discussed with clarity and precision.

Networks that Remember

That most intriguing aspect of human memory: its persistence in spite of continual loss of individual neurons over the lifetime of the individual has led many workers to the concept of distributed memory. (Longuet-Higgins 1968; Anderson, 1970, 1972; Cooper, 1974; Pribam et al., 1974; Kohonen, 1977). For a distributed memory (more like a hologram than a photograph) possesses in a very natural way the property of relative invulnerability to the loss of storage units: individual memory sites hold superimposed information concerning many events. In order to obtain a single event, information must be gathered from many sites. Loss of individual units decreases signal to noise ratios but does not lose items of information.

Further, in contrast to modern computers that perform large numbers of sequential operations very rapidly and very accurately, the central nervous system works slowly and probably not with enormous accuracy on the level of individual units, with cycle times that cannot be shorter than a few milliseconds. However we can make complex decisions in small parts of a second. This suggests very strongly that there is much parallel processing in the brain - an idea that is almost obvious on inspection of a component such as the retina.

It is now commonly thought that the synaptic junction may be a means to store information (memory, for example) as well as to transmit it from neuron to neuron. Large networks of neurons connected to other neurons via modifiable synaptic junctions provide the physiological substrate for the distributed parallel systems discussed here.

For a distributed memory it is the simultaneous or near simultaneous activities of many different neurons (the result of external or internal stimuli) that is of interest. Thus a large spatially distributed pattern of neuron discharges, each of which might not be very far from spontaneous activity, could contain important, if hard to detect, information. Let us consider the behavior of an idealized neural network (that might be regarded as a model component of a nervous system) to illustrate some of the important features of distributed mappings.

Consider N neurons 1, 2, ... , N, each of which has some spontaneous firing rate r_{jo}. (This need not be the same for all of the neurons, nor need it be constant in time.) We can then define an N-tuple whose components are the difference between the actual firing rate r_j of the jth neuron and the spontaneous firing rate r_{jo}:

$$f_j = r_j - r_{jo} \tag{1}$$

By constructing two such banks of neurons connected to one another (or even by the use of a single bank which feeds signals back to itself), we arrive at a simplified model as illustrated in Figure 1.1.

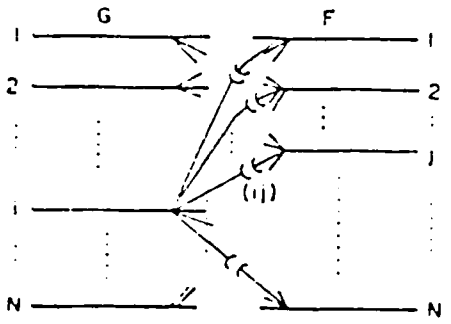


Fig. 1.

An Ideal Distributed Mapping.
Each of the N input neurons in F
is connected to each of the N output
neurons in G by a single ideal junction.
(Only the connections to i are drawn.)

The actual synaptic connections between one neuron and another are generally complex and redundant; we have idealized the network by replacing this multiplicity of synapses between axons and dendrites by a single ideal junction which summarizes logically the effect of all of the synaptic contacts between the incoming axon branches from neuron j

in the F bank and the dendrites of the outgoing neuron i in the G bank (Figure 1.2).

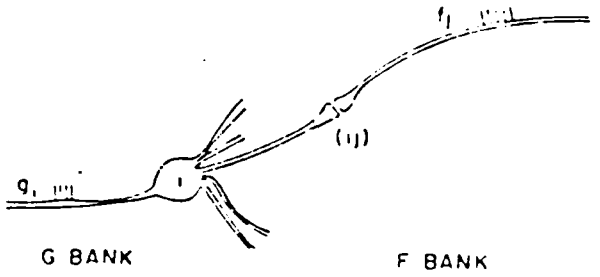


Fig. 2. An ideal synaptic junction.

Although the firing rate of a neuron depends in a complex and nonlinear fashion on the presynaptic potentials, there is usually a reasonably well defined linear region in which some very interesting network properties are already evident. We therefore focus our attention on the region above threshold and below saturation for which the firing rate of neuron i in G, g_i is mapped from the firing rates of all of the neurons f_j in F by:

$$g_i = \sum_{j=1}^{N} A_{ij} f_j . \qquad (2)$$

In doing this we are regarding as important average firing rates, and time averages of the instantaneous signals in a neuron (or perhaps a small population of neurons). We are further using the known integrative properties of neurons.

We may then regard $[A_{ij}]$ (the synaptic strengths of the N^2 ideal junctions) as a matrix or a mapping which takes us from a vector in the F space to one in the G space. This maps the neural activities $f = (f_1, f_2 \ldots f_N)$ in the F space into the neural activities $g = (g_1, \ldots g_N)$ in the G space and can be written in the compact form

$$g = Af \qquad (3)$$

It has been shown that the non-local mapping A can serve in a highly precise fashion as a memory that is content addressable and in which 'logic' is a result of association and an outcome of the nature of the memory itself. (Cooper, 1974)

To illustrate with a simple example, that illuminates the content addressable properties of the mapping, write:

$$A = \sum_{\mu} g^{\mu} \times f^{\mu}. \qquad (4)$$

Here g^{μ} and f^{μ} are output and input patterns of neural activity. The symbol, x, represents the 'outer' product between the input and output vectors. Although (4) is a well-known mathematical form, its meaning as a mapping among neurons deserves some discussion. The ijth element of A gives the strength of the ideal junction between the incoming neuron j in the F bank and the outgoing neuron i in the G bank (Figure 2).

Since

$$A_{ij} = \sum_{\mu} g_i^{\mu} f_j^{\mu}. \qquad (5)$$

the ijth junction strength is composed of a sum of the entire connectivity of the system as reflected in firing rates of the neurons connected to this junction. Each association however, is stored over the entire array of N X N junctions. This is the essential meaning of a distributed memory: Each event is stored over a large portion of the system, while at any particular local point many events are superimposed.

The fundamental problem posed by a distributed memory is the address and accuracy of recall of the stored patterns.

An arbitrary event, e, in the external world mapped by the sensory apparatus into the pattern of neural activity, f, will according to (3), generate the response, g = Af, in G.

(The pattern, f, might also be the result of some other internal pattern of neural activity.) If we equate recognition with the strength of this response, say the innter product (g,g), and if, for illustration, we define separated events as those that map into orthogonal vectors: $e^1 f_1$, $e^2 f^2$ ... $e^k f^K$ where

$$(f^\alpha , f^\beta) = \begin{matrix} 0 & \alpha \neq \beta \\ 1 & \alpha = \beta \end{matrix} \qquad (6)$$

then the mapping A will distinguish between those events it contains, the f^μ , $\mu = 1, 2, \ldots K$ and other events separated from these.

$$A f^\alpha = \sum_{\mu=1}^{K} g^\mu \times f^\mu f^\alpha = \sum_{\mu=1}^{K} g^\mu (f^\mu , f^\alpha)$$

$$= g^\alpha \quad \text{if } f^\alpha \text{ is one of the vectors } f1 \ldots f^K \qquad (7)$$

$$= 0 \quad \text{if } f^\alpha \text{ is not one of these vectors}$$

In this special situation, the content addressable, parallel distributed memory is as precise as a localized memory.

$$f^1 \rightarrow g^1$$

$$f^2 \rightarrow g^2 \qquad (8)$$

$$\vdots$$

$$f^k \rightarrow g^K$$

The properties of such a memory in more general circumstances, its ability to form associations, to map the external world, to create an 'animal logic' have been discussed elsewhere. (Cooper, 1974)

Long and short-term memory

The N2 junctions, A_{ij} contain the content of the distributed memory. It could be that a particular junction strength, Aij, is composed of several different components with different lifetimes thought of as corresponding to different physiological or anatomical effects (e.g., changes in numbers of presynaptic vesicles, changes in numbers of postsynaptic receptors. Changes in Ca^{++} levels and/or availability.

anatomical changes such as might occur in growth or shrinkage of spines). We then have the possibility that the actual memory content (even in the absence of additional learning) it will vary with time. For a two-component system we might have

$$A_{ij}(t) = A_{ij}^{(long)}(t) + A_{ij}^{(short)}(t). \qquad (9)$$

where $A_{ij}^{(t)}$ represents the memory at some time t. while $A_{ij}^{(long)}$ and $A_{ij}^{(short)}$ have long and short lifetimes. Thus in time $A_{ij}^{(short)}$, will decay, leaving $A_{ij}^{(t)} = A_{ij}^{(long)}$. Whether what is in the short-term memory component is transferred to the long-term component might be determined by some global signal- depending on the interest of the information contained in the short-term component.

From this point of view the site of long and short-term memory can be essentially identical. At any given time there is a single memory. The distinction between long and short-term memory is contained in the lifetime of the different components of A_{ij}.

Networks That Learn

We now ask how a mapping of the type A might be put into the network. The ijth element of A,

$$A_{ij} = \sum_{\mu\nu} c_{\mu\nu} g_i^{\mu} f_j^{\nu} \tag{10}$$

is a weighted sum over the j components of all mapped signals f^{ν} and the i components of the responses g_{μ} appropriate for recollection or association. Such a form could be obtained by additions with each input f and output g to the element A_{ij}:

$$\delta A_{ij} \sim g_i f_j \tag{11}$$

This δA_{ij} is proportional to the product of the differences between the actual and the spontaneous firing rates in the pre-and postsynaptic neurons i and j. [This is one realization of Hebb's form of synaptic modification (Hebb, 1949).] The addition of such changes to A for all associations g^{μ} X f^{ν} results finally in a mapping with the properties discussed in the previous section.

Synaptic modification dependent on inputs alone, of the type already directly observed in Aplysia (Kandel, 1976), is sufficient to construct a simple memory-one that distinguishes what has been seen from what has not, but does not easily separate one input from another. To construct a mapping of the form above, however, requires synaptic modification dependent on information that exists at different places on the neuron membrane-what we call two-(or higher-)point modification.

In order that this take place, information must be communicated from, for example, the axon hillock to the synaptic junction to be modified. This implies the existence of a means of internal communication of information within a neuron-in the above example, in a direction opposite to the flow of electrical signals (Cooper, 1974). The junction ij, for example, must have information of the firing rate f_j (which is locally available) as well as the firing rate g_i, which is somewhat removed (Figure 3). One possibility could be that the integrated electrical signals from the dendrites produce a chemical or electrical response in the cell body which controls the spiking rate of the axon and at the same time communicates (by backward spiking, for example) to the dendrite ends the information of the integrated slow potential.

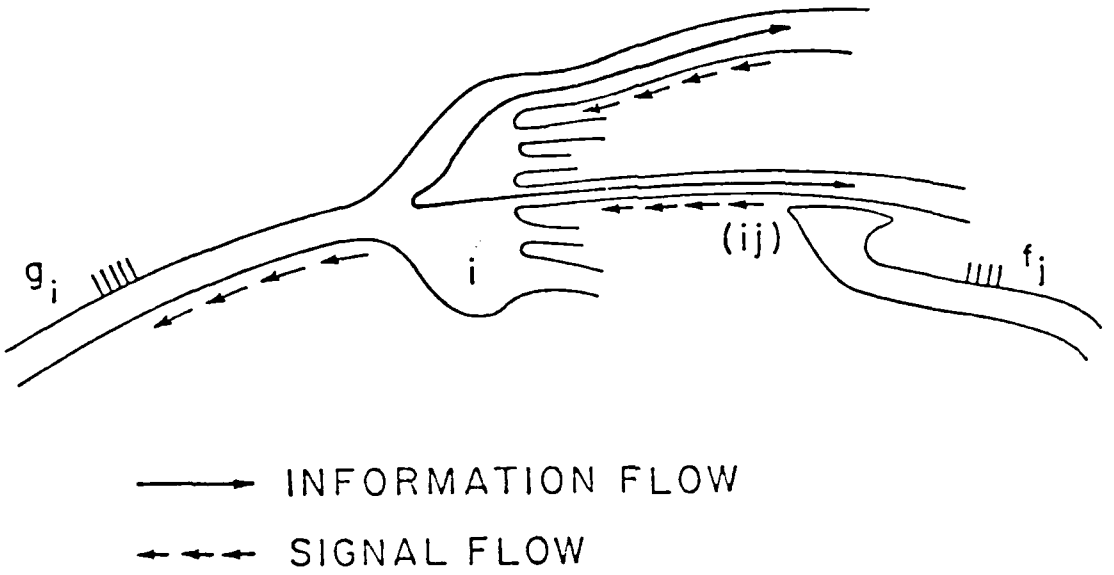


Figure 3.

Two Point Modification

Summary of Related Visual Cortex Experimental Data

The discussion above leads to a central issue: what is the principle of local organization that, acting in a large network, can produce the observed complex behavior of higher mental processes. There is no need to assume that such a mechanism -- believed to involve synaptic modification -- operates in exactly the same manner in all portions of the nervous system or in all animals. However, one would hope that certain fundamental similarities exist so that a detailed analysis of the properties of this mechanism in one preparation would lead to some conclusions that are generally applicable. We are interested in visual cortex because the vast amount of experimental work done in this area of the brain -- particularly area 17 of cat and monkey--strongly indicate that one is observing a process of synaptic modification dependent on the information locally and globally available to the cortical cells.

Experimental work of the last generation, beginning with the path-breaking work of Hubel and Wiesel (1959, 1962), has shown that there exist cells in visual cortex (areas 17, 18, and 19) of the adult cat that respond in a precise and highly tuned fashion to external patterns--in particular bars or edges of given orientation and moving in a given direction. Much further work (Blakemore and Cooper, 1970; Blakemore and Mitchell, 1973; Hirsch and Spinelli, 1971; Pettigrew and Freeman, 1973) has been taken to

indicate that the number and response characteristics of such cortical cells can be modified. It has been observed in particular (Imbert and Buisseret, 1975; Blakemore and Van Sluyters, 1975; Buisseret and Imbert, 1976; and Fregnac and Imbert, 1977, 1978), that the relative number of cortical cells that are highly specific in their response to visual patterns varies in a very striking way with the visual experience of the animal during the critical period.

Most kittens first open their eyes at the end of the first week after birth. It is not easy to assess whether or not orientation selective cells exist at that time in striate cortex: few cells are visually responsive and the response's main characteristics are generally "sluggishness" and fatigability. However, it is quite generally agreed that as soon as cortical cells are reliably visually stimulated (e.g., at 2 weeks), some are orientation selective, whatever the previous visual experience of the animal (eg. Hubel and Wiesel, 1963; Blakemore and Van Sluyters, 1975; Buisseret and Imbert, 1976; Fregnac and Imbert, 1978).

Orientation selectivity develops and extends to all visual cells in area 17 if the animal is reared, and behaves freely, in a normal visual environment (NR): complete "specification" and normal binocularity (about 80% of responsive cells) are reached at about 6 weeks of age (Fregnac and Imbert, 1978). However, if the animal is reared in total darkness from birth to the age of 6 weeks (DR), none or few orientation selective cells are then

recorded (from 0 to 15% depending on the authors and the classification criteria); however, the distribution of ocular dominance seems unaffected (Blakemore and Mitchell, 1973; Imbert and Buisseret, 1975; Blakemore and Van Sluyters, 1975; Buisseret and Imbert, 1976; Leventhal and Hirsch, 1980; Fregnac and Imbert, 1978). In animals whose eyelids have been sutured at birth, and which are thus binocularly deprived of pattern vision (BD), a somewhat higher proportion (from 12 to 50%) of the visually excitable cells are still orientation selective at 6 weeks (and even beyond 24 months of age) and the proportion of binocular cells is less than normal (Wiesel and Hubel, 1965; Blakemore and Van Sluyters, 1975; Kratz and Spear, 1976; Leventhal and Hirsch, 1977; Watkins, et al., 1978).

Of all visual deprivation paradigms, putting one eye in a competitive advantage over the other has probably the most striking consequences. If monocular lid-suture (MD) is performed during a "critical" period (ranging from about 3 weeks to about 12 weeks), there is a rapid loss of binocularity to the profit of the open eye (Wiesel and Hubel, 1963, 1965). At this stage, opening the closed eye and closing the experienced one may result in a complete reversal of ocular dominance (Blakemore and Van Sluyters, 1974). A disruption of binocularity that does not favor one of the eyes may be obtained, for example, by provoking an artifical strabismus (Hubel and Wiesel, 1965) or by an alternating monocular occlusion, which gives both eyes an equal amount of visual stimulation (Blakemore, 1976). In what follows, we call this uncorrelated rearing (UR).

These results seem to us to provide direct evidence for the modifiability of the response of single cells in the cortex of a higher mammal according to its visual experience. Depending on whether or not patterned visual information is part of the animal's experience, the specificity of the response of cortical neurons varies widely. Specificity increases with normal patterned experience. Deprived of normal patterned information (dark-reared or lid-sutured at birth, for example) specificity decreases. Further, even a short exposure to patterned information after six weeks of dark-rearing can reverse the loss of specificity and produce an almost normal distribution of cells.

We do not claim and it is not necessary that all neurons in visual cortex be so modifiable. Nor is it necessary that modifiable neurons are especially important in producing the architecture of visual cortex. It is our hope that the general form of modifiability we require to construct distributed mappings manifests itself for at least some cells of visual cortex that are accessible to experiment. We thus make the conservative assumption that biological mechanisms, once established will manifest themselves in more or less similar forms in different regions. If this is the case, modifiable individual neurons in visual cortex can provide evidence for such modification more generally.

Modification of Cortical Synapses: Local and Global Variables

Cortical neurons receive afferents from many sources. In visual cortex (layer 4, for example) the principle afferents are those from the lateral geniculate nucleus and from other cortical neurons. This leads to a complex network that we have analyzed in several stages.

In the first stage we consider a single neuron with inputs from both eyes (Figure 4).

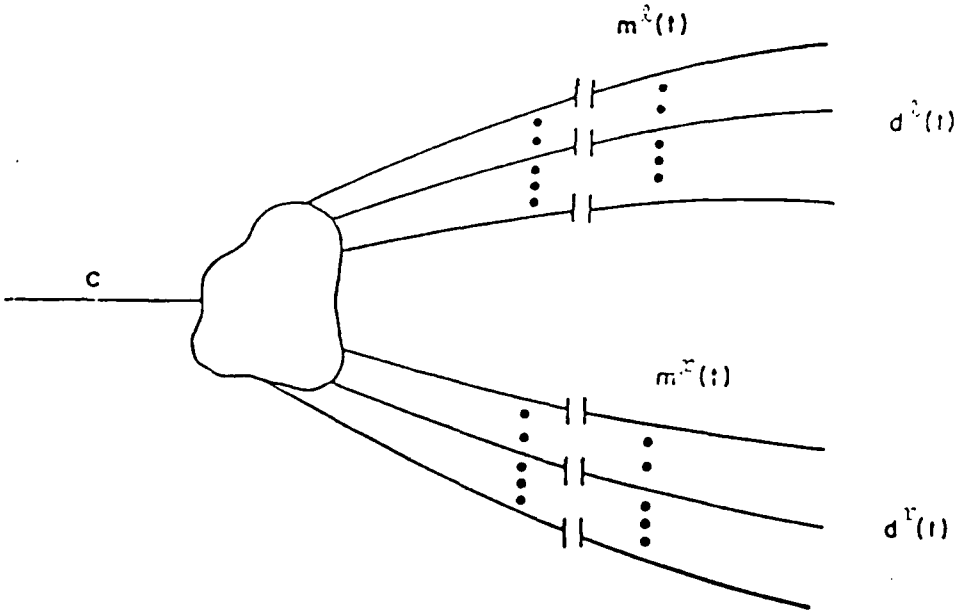


Figure 4

A Model Neuron

Here d^{ℓ}, d^{r}, m^{ℓ}, m^{r} are inputs and synaptic junctions from left and right eyes. The output of this neuron (in the linear region) can be written

$$c = m^{\ell}.d^{\ell} + m^{r}.d^{r} \tag{12}$$

This means that the neuron firing rate (in the linear region) is the sum of the inputs from the left eye multiplied by the appropriate left-eye synaptic weights plus the inputs from the right eye multiplied by the appropriate right-eye synaptic weights. Thus the neuron integrates signals from the left and right eyes.

According to the theory presented by Bienenstock, Cooper and Munro, 1982 (BCM) these synaptic weights modify as a function of local and global variables. To illustrate we consider the synaptic weight mj.

Its change in time, $\dot{m}_j$, is given below:

$$\dot{m}_j = F(d_j \ldots m_j ; d_k \ldots c; \bar{c} \ldots ; X, Y, Z). \tag{13}$$

Here variables such as $d_j \ldots m_j$ are designated local. These represent information (such as the incoming signal, d_j, and the strength of the synaptic junction, m_j) available locally at the synaptic junction, m_j. Variables such as $d_k \ldots c$ are designated

quasi-local. These represent information (such as c, the firing rate of the cell, or d_k, the incoming signal to another synaptic junction) that is not locally available to the junction m_j but is physically connected to the junction by the cell body itself--thus necessitating some form of internal communication between various parts of the cell and its synaptic junctions. Variables such as c (the time averaged output of the cell) are averaged local or quasi-local variables. Global variables are designated X,Y,Z... These latter represent information (e.g. presence or absence of neurotransmitters such as norepinephrine or the average activity of large numbers of cortical cells) that is present in a similar fashion for all or a large number of cortical neurons (distinguished from local or quasi-local variables presumably carrying detailed information that varies from synapse to synapse).

In a form relevant to this discussion, BCM modification can be written

$$\dot{m}_j = \phi(c, \bar{c}; X, Y, Z...)d_j \qquad (14)$$

so that the j^{th} synaptic junction, m_j, changes its value in time as a function of quasi-local and time-averaged quasi-local variables, c and $\bar{c}$, as well as global variables X,Y,Z, through the function, ϕ , and a function of the local variable d_j. The crucial function, ϕ , is shown in Figure (5).

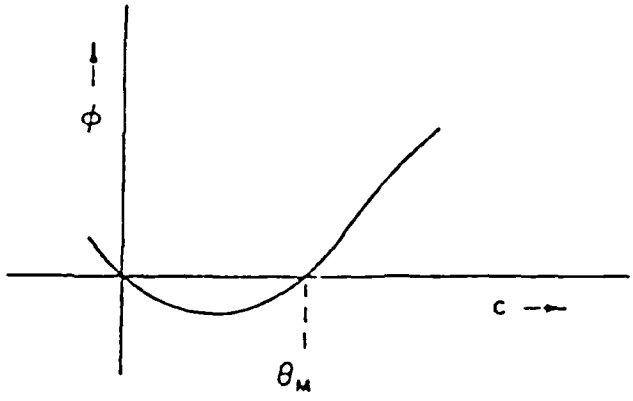


Fig. (5)
The BCM Modification Function

What is of particular significance is the change of sign of ϕ at the modification threshold, θ_M, and the non-linear variation of θ_M with the average output of the cell c. In a simple situation

$$\theta_M = (\bar{c})^2 \qquad (15)$$

The occurance of negative and positive regions for ϕ drives the cell to selectivity in a 'normal' environment. This is so because the response of the cell is diminished to those patterns for which the output, c, is below threshold (ϕ negative) while the response is enhanced to those patterns for which the output, c, is above threshold (ϕ positive). The non-linear variation of the threshold with the

average output of the cell, $\bar{c}$, places the threshold so that it eventually separates one pattern from all of the rest. Further it provides the stability properties of the system.

A detailed analysis of the consequences of this form of modification is given in BCM. The results (as modified in the network analysis outlined next) are in general agreement with what we might call classical experiments of the last generation. Neurons in normal (patterned environments) become selective and binocular. In various deprived environments (e.g. monocular or binocular deprivation) the theoretical behavior follows the experimental results.

Extension to Networks

To better confront these ideas with experiment the single neuron discussed above, must be placed in a network with anatomical and physiological features of the region of interest. For visual cortex this suggests a network in which inhibitory and excitatory cells receive input from the lateral geniculate nucleus (LGN) and from each other. A simplified form of such a network, a first-order representation of the anatomy and physiology of layer IV of cat visual cortex (Figure 6) has been studied by Scofield and Cooper, (in Press).

In a network generalization of Eq. (12), we write

$$c_i = m_i^{\ell} \cdot d^{\ell} + m_i^{r} \cdot d^{r} + \sum_j L_{ij} c_j \qquad (16)$$

where L_{ij} are the intracortical connections.

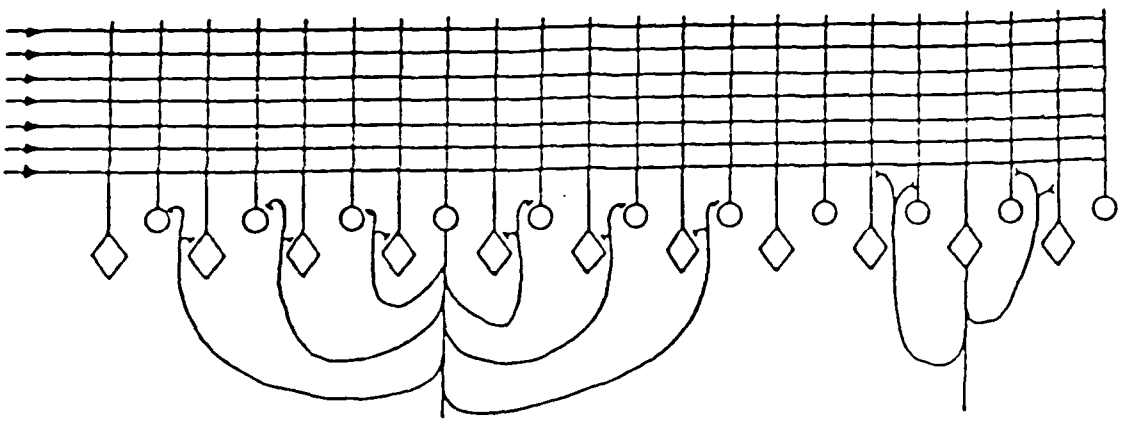


Fig. 6

A simplified neural network. Shown are the two cell types: inhibitory represented by circles, and excitatory by diamonds. Geniculate afferents enter at the top of the figure and synapse with all cells in the network at the intersection of the horizontal and vertical fibers. Also shown are intracortical fiber for each cell type. The exact ratio of inhibitory to excitatory cells is not important.

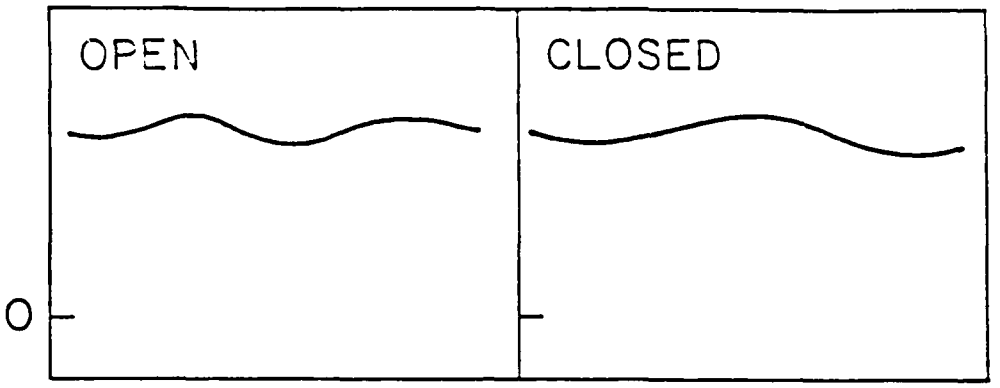
Analysis by Scofield and Cooper of the network along lines similar to that of the single cell analysis described above shows that under proper conditions on the intracortical synapses, the cells converge to states of maximum selectivity with respect to the environment formed by the geniculate signals. Their conclusions are therefore similar to those of BCM with explicit further statements concerning the independent effects of excitatory and inhibitory neurons on selectivity and ocular dominance. For example, shutting off inhibitory cells lessens selectivity and alters ocular dominance. The inhibitory cells may be selective but there is no theoretical necessity that they be so.

A mean field approximation to the above network (Cooper and Scofield, to be published) shows that if the average effect of intracortical connections results in inhibition of individual cells, then in monocular deprivation, the geniculocortical synapses to the cell will converge to non-zero states that give, as the result of stimulation of the closed eye, total responses that are zero. However, the fact that the geniculocortical states are non-zero means that the removal of cortical inhibition through the chemical blocking of inhibitory synapses would uncover responses from previously non-responsive cells. This result is in accord with the experimental observation of 'masked synapses' after the removal of the inhibitory effects of GABA with the blocking agent bicuculline (Duffy et al. 1976, Sillito et al. 1980).

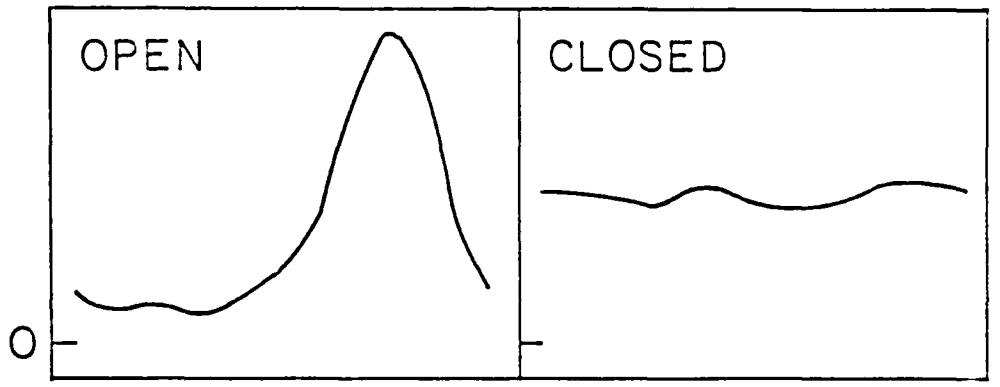
An unexpected consequence of this theory is a connection between selectivity and ocular dominance. The analysis given in BCM and extended in the mean-field network theory shows that in monocular deprivation, non-preferred inputs presented to the open are a necessary part of the suppression of deprived eye responses. It follows that the more selective the cell is to the open eye (increasing the probability of non-preferred inputs) the more closed eye will be driven to zero, thus increasing the dominance of the open eye.

For an experimental test of these ideas it is important to determine what happens <u>during</u> the ocular dominance shift produced by monocular deprivation. Consider the experimental situation in which monocular experience follows a period of dark rearing. [Such experiments are presently being performed by Saul and Daniels (private communication)]. During dark rearing it is known that most area 17 cells become less responsive (sluggish) and lose their selectivity and that some (perhaps 20%) become visually non-responsive.

Our theoretical analysis indicates that in the course of monocular experience, those cells that have become visually non-responsive during the dark rearing will first show an increase in responsiveness to the open eye followed by the development of selectivity. Those cells that have survived the period of dark rearing binocular and a-specific will exhibit a progression in which selectivity to the open eye is increased while maintaining their response (often non-selective) to the closed eye. This should result in two sequences shown in figures 7a and 7b.



INITIAL



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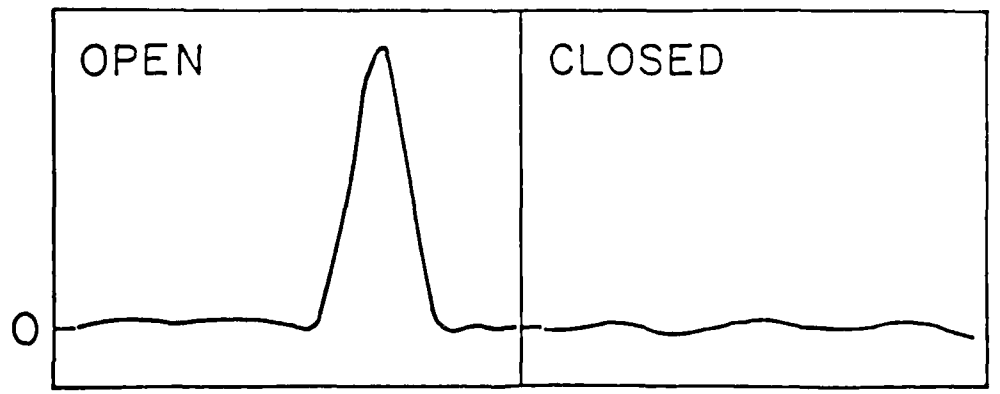
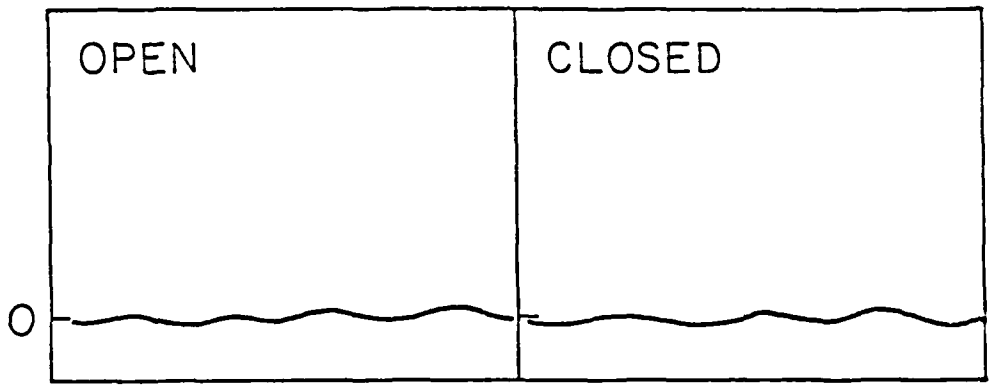


Final

Fig. (7a)

Progression of development of selectivity and ocular dominance. Note that selectivity develops for responsive binocular aspecific cells for the open eye before the response to the closed eye is driven to zero.



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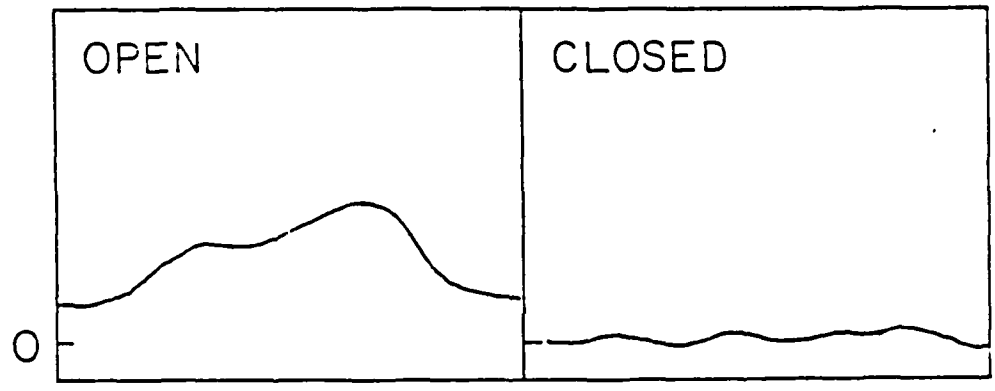

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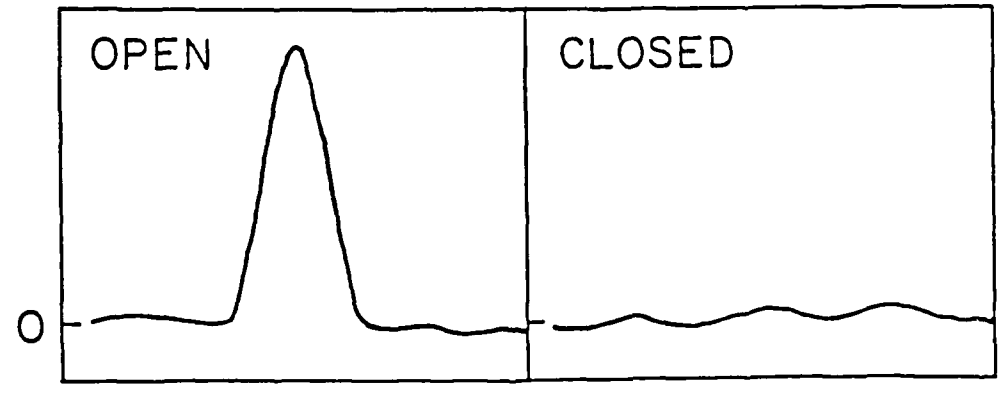

Final

Fig. (7b)

Progression of development of responsiveness and selectivity. Note that responsiveness to the open eye develops before, or along with, selectivity.

These results are obtained without assuming that the intracortical inhibitory synapses are very responsive to visual experience. Learning can occur entirely among the excitatory LGN-cortical synapses. Another point of view is espoused, for example, by Rauschecker and Singer (1981). They suggest that since cells lose their orientation specificity when binocularly deprived of pattern vision, and since it has been shown that inhibitory connections play a major role in determining orientation selectivity. (Sillito, 1975), the cortical inhibitory synapses must suffer more than excitatory ones.

These conflicting ideas led us to perform experiments on changes in inhibitory activity due to visual experience (Bear et al.1985), and described in the next section. They indicate that one measure of cortical inhibition is relatively constant even during dramatic manipulations of the visual environment.

Experimental Test of Changes in Inhibitory Activity Due to Visual Experience

One of the consequences of the network theory discussed in the previous section, is that experimental results that have been obtained in visual cortex over the last generation can be explained primarily by modification of lateral geniculate (LGN) to cortex synapses with minimum changes among intra-cortical synapses. Thus the possibility is opened that most learning takes place in the LGN synapses. This somewhat surprising result has as one consequence the possibility of great simplification in the analysis of network modification.

An alternate hypothesis that has been considered for some time is that intracortical synapses bear heavy responsibility for modification in cortical circuitry during learning. In particular it has been suggested that ocular dominance shifts in monocular deprivation are due to increased activity of GABAergic neurons, the open eye supressing the closed. Sillito (1975) documented in normal cats that visually unresponsive cells may be "unmasked" by iontophoretic bicuculline. Thus, it is not unreasonable to speculate that many of the unresponsive cells in visually deprived kittens are being suppressed. Together, these data suggest as a possible hypothesis that in kitten striate cortex the GABAergic neurons respond to sensory deprivation by forming new synapses. This hypothesis implies that the density or strength of GABAergic synapses will increase in zones of cortex that are deprived of a normal thalamic input; in the case of monocular deprivation, these

zones correspond to the closed-eye ocular dominance columns and to the monocular segment contralateral to the deprived eye. On the other hand, the theory described above suggests that there will be minimal response of GABAergic neurons to sensory deprivation. This hypothesis has been put to test in a recent series of experiments (Bear et al. 1985).

To examine the distribution of GABAergic synapses, Bear et al immunocytochemically localized GAD in sections of striate cortex. While immunocytochemistry is not a quantitative measure, they reasoned that changes restricted to deprived ocular dominance zones should be readily detected with this method. As a quantitative estimate of GABAergic synapse density, they biochemically measured GAD activity in homogenates of striate cortex.

They found no evidence for a change in the distribution of GAD positive puncta in 12 unilaterally enucleated kittens. The band of layer IV puncta remained uniform even though the periods of monocular deprivation examined would all be sufficient to cause a physiological ocular dominance shift in striate cortex GAD immunoreactivity was unchanged even under conditions that produced alterations in the level of the metabolic enzyme, cytochrome oxidase. Measurements of GAD activity showed no consistent or significant difference between either the binocular segments of enucleated and control kittens, or the monocular segments of enucleated animals.

This conclusion is in striking agreement with network analysis which, as mentioned above, suggests that inhibitory synapses are much less modified by experience than excitatory synapses. In addition to its implications for the 'site of learning' such a hypothesis leads to important simplifications in the analysis of complex networks.

Possible Candidates for Global Controllers

Any theory of learning generally requires global as well as local controls. As discussed previously, local controls are those that determine detailed changes of individual synaptic junctions while global information would be expected to influence all or large numbers of synaptic junctions in the same way. From the point of view of a learning theory, there must be some way to distinguish more interesting from less interesting input. Experimentally it is known that certain areas of cortex (visual, auditory, somatic sensory) exhibit plasticity during early critical periods, but not during adulthood.

For example, most neurons in the visual cortex of newborn kittens (and normal adult cats as well) are activated equally well by both eyes. During the critical period (three weeks to three months in cats), monocular lid suture or misalignment of the eyes (called strabismus) leads to the domination of cortical cells by one eye. In contrast, adult cats, that are given monocular visual experience when they are older than six months of age, remain unaffected by the imbalance of visual inputs; adult cortical neurons remain binocularly activated.

A major question can be formulated as follows: What are the global factors acting singly or in combination that affect the development of synapses in cortex, or, following the argument of the previous sections, the LGN-cortical synapses.

In recent years it has been suggested that catecholamines (CA) are required for neuronal plasticity in the neocortex. One test of this hypothesis has been made in a series of experiments performed by Kasamatsu and Pettigrew (1976, 1979) and Kasamatsu et al. (1979, 1981) who used the monocular deprivation paradigm with kitten visual cortex as a test system. In their control kittens they found the usual effect of monocular deprivation during the critical period--within a week the majority of cells lost their normal binocular responsiveness and could be driven only by stimulation of the non-deprived eye. But, in animals given the neurotoxin 6-hydroxydopamine (6-OHDA) to deplete cortical CAs, the ocular dominance shift failed to occur and cells remained binocularly driven.

In later experiments Kasamatsu and Pettigrew pioneered the use of miniature osmotic pumps to infuse 6-OHDA continuously to local regions of cortex in one hemisphere while they used the other hemisphere as a control by perfusing only the vehicle for the 6-OHDA. Following monocular deprivation, normal plasticity was again disrupted in CA depleted cortex as indicated by the lack of a shift in ocular dominance of visual cells. Because both noradrenergic and dopaminergic fibers project to the visual cortex, Kasamatsu et al. also used the minipumps to add norepinephrine (NE) to the cortex previously depleted of CAs to demonstrate that NE, itself can restore plasticity. This evidence suggests that catecholamines, especially NE, are necessary for

the cortical changes observed in kittens which have restricted vision during the critical period.

However, the relationship between static NE levels and plasticity is not simple. In one experiment, (Bear and Daniels. 1983; Rear et al. 1983) cortical catecholamines were permanently depleted in newborn kittens by intra peritoneal injections of 6-OHDA. Biochemical analysis demonstrated severe reduction of NE levels; but in this experiment plasticity, as evidenced by ocular dominance shift, remained intact. In the neonatal experiments kittens received 6-OHDA at birth and were monocularly deprived for 7 days at about 5 weeks of age. The minipump-kittens received 6-OHDA continuously for the 7 days of monocular deprivation. Comparison of the two paradigms suggests the possibility that loss of plasticity is not caused by depletion of NE alone.

Thus, despite Kasamatsu's success in demonstrating support for the NE hypothesis, questions have arisen. The above experiments show that early depletion of cortical NE does not, by itself prevent the later ocular dominance shift after monocular deprivation. Other experiments confirm this conclusion. Daw et al.(1984) depleted cortical NE by section of the locus coeruleus fiber bundle near lateral hypothalmus and found no diminution of the ocular dominance shift after monocular deprivation. Videen et al.(1984) recorded no difference in the reaction of kitten and adult cat visual cortex neurons to

iontophoretically applied NE. Adrien et al.(1982) observed no lack of shift after lesion of the locus coeruleus itself; and that group was unable to reproduce Kasamatsu and Pettigrew's, 1979. finding that intra-ventricular injection of 6-OHDA prevents ocular dominance shift. All of these results reinforce the idea that NE is not the only factor in the global control of learning.

In addition to the norepinephrine (NE) system, several lines of evidence suggest that the cholinergic (ACh) system may also serve as a global modulator of cortical function. Similar to the locus coeruleus-NE system, the basal forebrain cholinergic (ACh) system has a widespread input to cortex that stands in marked contrast to the highly organized thalamocortical systems that provide specific sensory input to cortex. In addition several findings link both the NE and ACh systems to acquisition and storage processes related to learning and memory.

While these global cortical inputs have been related to memory and learning, the specific cellular mechanisms of ACh and NE function are unclear. Present evidence indicates that both systems may modulate the response of cortical neurons to specific sensory inputs. NE appears to improve the signal to noise ratio of sensory responses both in somatic sensory and in the primary visual cortex and NE may potentiate the action of both excitatory and inhibitory transmitters. These effects of NE are mediated through alpha adrenergic receptors which appear to be concentrated in the deeper layers (IV-VI) of cortex.

The cholinergic system may function in a manner similar to NE. Application of low levels of ACh enhances the excitatory response of cortical neurons to glutamate and modifies the task related discharge of cortical neurons during behavior. ACh has also been shown to modify the membrane input resistance of cortical neurons for at least 1.5 hours. The slow onset, long duration of action, and sensitizing effects of ACh are all consistent with the conclusion that the cholinergic system is mainly a modulator of cortical activity. Thus, the evidence to date suggest that both NE and ACh may play a modulatory role in cortex.

This view has been reinforced by recent work of Bear and Singer (Private communication) which indicates that 6-OHDA. in addition to destroying NE neurons, also competitively binds with muscarinic cholinergic receptors to prevent ACh effects on cortical neurons. In addition Bear and Singer have shown that the simultaneous diminution of both ACh and NE appears to prevent the ocular dominance shift in monocular deprivation while the diminution of either ACh or NE (and not both) does not prevent this shift.

These results may enable a resolution of the apparent contradictions in previous NE experiments discussed above and, in addition, suggest the fascinating possibility that ACh and NE act together to provide a global modulator for plasticity.

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